UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/805,099	03/19/2004	Chunhui Xu	099/004P	7715

22869 7590 06/25/2008

GERON CORPORATION
Attn. David J. Earp
230 CONSTITUTION DRIVE
MENLO PARK, CA 94025

EXAMINER	
NOBLE, MARCIA STEPHENS	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
06/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/805,099	XU ET AL.	
	Examiner	Art Unit	
	MARCIA S. NOBLE	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,7,9 and 10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,7,9 and 10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/4/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 1-4, 6, 7, 9, and 10 are pending. Claims 1 and 4 are amended and claims 5 and 8 are canceled, by the amendment filed 3/4/2008. Claims 1-4, 6, 7, 9, and 10 are under consideration.

Information Disclosure Statement

2. The information disclosure statement filed 5/8/2008 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The examiner is able to retrieve and consider the U.S. patents and WO documents listed, but copies of the non-patent literature documents could not be located. Goh et al (2005), Khamsi et al (2005), Laflamme et al (2005), Strauer et al (2005), Van Laake et al (2005), Xiao et al (2003), and Xu et al (2006) were not provided and therefore could not be considered.

Withdrawn Rejections/Objections

4. The objection to claim 1, objected to for reciting in b) "differentiate into areas", as set forth in the Office Action, mailed 10/9/2007, is withdrawn.

The rejection of claims 1-10, under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of generating cardiomyocytes and cardiomyocyte precursor cells from human embryonic stem (hES) cells obtained from a

human blastocyst comprising initiating differentiation of the hES by forming embryoid bodies (EB) in suspension culture wherein some hES cells of the EB differentiate into cells that undergo spontaneous contraction, harvesting the differentiated cells that demonstrate spontaneous contraction, separating the harvested cells into factions by gradient density centrifugation, collecting the fractions with a density of between ~1.05 and ~1.075 g/mL, and isolating the cells from the collected fractions that express cardiac tronin I (cTnI), cardiac troponin T (cTnT), atrial natriuretic factor (ANF) or α-cardiac myosin heavy chain (MHC), thereby generating a cell composition comprising cardiomyocytes and cardiomyocyte precursor cells, and while being enabled for the above disclosed method wherein initiating differentiation occurs in a growth environment comprising serum, activin, insulin-like growth factor (IGF) and TGFβ , does not reasonably provide enablement for 1) a method of generating cardiomyocytes comprising collecting cells from any fraction of the gradient density centrifugation; 2) a method of generating cardiomyocytes comprising by differentiating hES cells in a growth environment comprising any morphogen and any growth factors and without serum; and 3) a method of generating a cell composition containing cardiomyocytes or cardiomyocytes precursor cells only, as set forth in Office Action, mailed 10/9/2007, is withdrawn.

The rejection of claims 1, 2, 6-8 as provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 and 16 of copending Application No. 11/085,899, as set forth in the Office Action, mailed 10/9/2007, is withdrawn.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 1, 2, 4, and 7 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 8-12 of copending Application No. 11/086,709. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed inventions have overlapping scope.

Applicant states that the instant rejection is provisional and if copending application becomes allowable prior to allowance of the current claims, Applicant will address the rejection on their merits or will file a terminal disclaimer. Applicant's statement is acknowledged and the rejection is maintained.

6. Claims 1-4, 7, and 10 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10, 12-18, and 20 of copending Application No. 11/040691

Applicant states that the instant rejection is provisional and if copending application becomes allowable prior to allowance of the current claims, Applicant will address the rejection on their merits or will file a terminal disclaimer. Applicant's statement is acknowledged and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4, 6, 7, 9, and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Doevendans et al (J Mol Cell Cardiol 32:839-851, 2000, of record), in view of Schuldiner et al (PNAS 97(21):11307-11312, 2000; of record), Sugi and Lough (Dev Biol 168:567-574, 1995; of record), Thomson et al (Science 282:1145-1147, 1998), and Nair and Nair (Indain J Exp Biol 35(5):451-456, 1997).

The instant invention is drawn to a method comprising initiating differentiation of hES cells by forming EB in suspension culture wherein the differentiated cells undergo spontaneous contraction, harvesting the differentiated cells, enriching the cardiomyocytes by density centrifugation, and collecting cell fractions that cells that express cardiac specific markers, cTnI, cTnT, ANF, or MHC. Narrowing claims specify that the EB be plated on a surface coated with gelatin or extracellular matrix, be differentiated in a growth environment activin, IGF, and TGF-beta. Narrowing embodiments also specify that the cells be further subjected to density centrifugation, that the collected cells be cultured in medium containing a compound capable of forming a high energy bond, an acyl group carrier molecule, and a cardiomyocytes calcium channel modulator and/or containing creatine, carnine, or taurine.

Doevendans et al teaches a method of initiating differentiation of mouse ES cells by initiating differentiation of the mES cells by forming EB in suspension culture, culturing the initiated cells so that they differentiate into cells that undergo spontaneous contraction, harvesting the differentiated cells, enriching the harvested cells by density

centrifugation, collecting the cell fractions that comprise cells expressing cardiac cell markers, and isolating the cells that express cardiac specific markers using immunochemistry (p. 840, par bridging col 1 and 2). Doevendans et al specifically use a Percoll density gradient wherein differentiated, spontaneously contracting cells are collected from between layers that were 1.09 g/ml to 1.07 g/ml (col 2, lines 18-24). The EBs and differentiated cells were cultured on gelatin in the presence of 20% fetal calf serum (col 2, lines 25-30). The general growth media in which the cells and EB were cultured were high glucose DMEM media (p. 840, col 1 last par, lines 3-6). Because the DMEM media contains high glucose, the media encompasses a media that has a compound capable of forming high energy phosphate bonds and an acyl group carrier molecule. Immunocytochemistry with atrial and ventricular myosins was also used to verify the cardiomyocytes lineage of the cells (p. 841, col 2, par 3). Doevendans do not explicitly teach that the cell fractions contain cells that express cTnI, cTnT or ANF. However because theses genes are cardiomyocyte specific genes, implicitly the fractions collected comprise cardiomyocytes that express these cardiomyocyte specific genes. Doevendans et al do not teach culturing in the presence of activin, IGF, and TGF-beta. Doevendans et al do not teach the use of hES cells. Doevendans et al do not teach culturing in medium containing a cardiomyocytes calcium channel modulator.

Schuldiner et al teach the culture of hES cells to form EB to initiate differentiation of the hES cells. After 5 days of EB culture, the EB cells are dissociated and the initiated cells are subjected to different growth factors to further drive differentiation down adult cell lineages (p. 11308, Fig 1 A). Schuldiner et al teach that culturing EB

intiated hES cells in the presence of activin-A and TGF-beta drive the hES cells to differentiate into cells of a mesodermal lineage and ultimately into muscle and heart cells (p. 11311, col 1, last par, lines 5-7 and Figure 4). Schuldiner et al teach that the ability to differentiate cells along specific cell lineages would be useful for further research in developmental biology and medical applications including cell transplantation (p. 11310, col 1, lines 7-10). Therefore, Schuldiner et al provides motivation to use hES cells in a cell differentiation method that differentiates hES cell down a mesodermal/cardiac linage.

Sugi and Lough teach a method of culturing mouse embryonic precardiac myocytes explants in the presence of activin-A, FGF-2, and insulin (p. 568, col 1, line 13 to col 2, line 19). Culturing mouse embryonic precardiac myocytes in the presence of activin-A, FGF-2, and insulin results in explants that exhibited synchronous contractions and expressed cardiac RNA (see abstract; p. 570, Fig 2 and p. 571, Fig 3). These data demonstrate that culturing with activin-A, FGF2 and insulin drives differentiation in an embryonic cardiomyocytes precursor cell and therefore provides motivation to include in cultured to generate cardiomyocytes from embryonic cells.

Similarly, Thomas et al teach that elucidating the mechanism that control differentiation will facilitate the effective differentiation of hES cells to specific cell types. The standardized production of large, purified populations of euploid human cells such as cardiomyocytes and neurons will provide a potentially limitless source of cells for drug discovery and transplantation therapies (p. 1146, col 3, last par, line 1 to p. 1147,

col 1, line 1). Therefore, Thomas et al provides motivation to more specifically use hES cells in a method that differentiates ES cell into cardiomyocytes.

Nair and Nair teach that culturing cardiomyocytes in the presence of the calcium ion chelator, EGTA, and taurine in the media for culturing cardiomyocytes improves the yield of ventricular myocardial cells that are Ca(2+)-tolerant (see abstract). Therefore, Nair and Nair teach the use of calcium chelator and taurine in cardiomyocyte media and a motivation to use them in the media (i.e. – to increase the yield of ventricular myocardial cells).

At the time of the invention, it would have been obvious to an artisan of ordinary skill that they could combine the methods of generating cardiomyocytes from mES cell taught by Doevendans with a method of differentiating hES cells as taught by Schuldiner et al to produce human cardiomyocytes. Schuldiner et al teaches that inclusion of activin and TGF-beta in the media will successfully drive the hES to differentiate into a mesodermal or cardiac cell lineage, and Sugi and Lough provide further support for the inclusion of activin-A , IGF, and TGF-beta because these growth factors have been demonstrated to differentiate mES cell into cardiomyocytes. Therefore, an artisan would have a reasonable expectation that activin A, IGF, and TGF-beta will also differentiate hES cell into cardiomyocytes. An artisan could include a calcium chelator and taurine in the media to improve the yield of ventricular cardiomyocytes, as taugh by Nair and Nair as well. An artisan would be motivated combine the teaching of Doevendans et al, Schuldiner et al, Sugi and Lough, and Nair and Nair to produce a method of generating cardiomyocytes from hES cell because it

would allow for the standardized production of a large, purified population of human cardiomyocytes that will provide a potentially limitless source of cells for drug discovery and transplantation therapies, as taught by Thomson et al. An artisan would have a reasonable expectation of success of producing human cardiomyocytes using the teachings of Doevedans et al, Schuldiner et al, Sugi and Lough, and Nair and Nair, because the differentiation methods for the production of human cardiac cells and cardiomyocytes were established in the art, as exemplified by Doevendans et al and Schuldiner et al. Therefore, because the art teaches a means of generating cardiomyocytes from hES cell and because the art provides a motivation to combine the teaching of the art with a reasonable expectation of success, the invention of the instant claims are rendered obvious by the art of Doevedans et al, Schuldiner et al, Sugi and Lough, and Nair and Nair.

Comment

8. As discussed in the 103a rejection above, step e of claim 1 is inherent to step d because the cell fractions produced in step d inherently express the cardiac specific genes of step "e." Amending claim 1 to encompass an active step that isolates the cells expressing the cardiac specific markers listed in step "e", may be remedial for overcoming the obviousness rejection above.

9. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch, Ph.D./
Primary Examiner, Art Unit 1632

Marcia S. Noble